



# LanroNET — A Non-Interventional Prospective Study to Assess the Resource Utilisation and Cost of Lanreotide Autogel 120 mg in the Population of Polish Patients with Symptomatic Neuroendocrine Tumours

LanroNET — nieinterwencyjne badanie prospektywne oceniające wykorzystanie zasobów medycznych i koszty Lanreotide Autogel 120 mg w populacji polskich pacjentów z objawowymi guzami neuroendokrynnymi

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## Abstract

**Introduction:** The primary objective of the LanroNET study was to evaluate the resource utilisation and cost of symptomatic treatment of patients with neuroendocrine tumours (NET) using lanreotide autogel 120 mg.

**Material and methods:** LanroNET was a multicentre, non-interventional, prospective study conducted at 12 clinical centres in Poland. Eligible patients were adults with symptomatic NET treated with lanreotide autogel 120 mg at least three months before enrolment. During 24-months of observation of real clinical practice, data on medical resource utilisation and the therapy course of patients with symptomatic NET were collected.

**Results:** Fifty-four patients with symptomatic NET were enrolled. The median time of lanreotide exposure was 1.7 years (range: 0.0–2.2). Thirty-three patients completed the study; the most frequent known cause of discontinuation (8/16) was disease progression. The mean cost of consumed resources without the cost of pharmacotherapy was estimated at PLN 26,307/EUR 6030.35 per year. During the study, the mean (SD) interval between injections was 31.7 days (6.7). At the end of observation — after 24 months of follow-up, seven patients were on a 42-day regimen. The average real-world cost of lanreotide autogel 120 mg was PLN 4216.30/EUR 966.49 per patient/28 days from the public payer and patient perspective and was lower by PLN 554.14/EUR 127.02 than the cost for the standard 28-day dosing interval.

**Conclusions:** LanroNET is the first two-year observational study of patients with symptomatic NET evaluating the cost of every-day clinical practice and lanreotide autogel treatment in Poland. (Endokrynol Pol 2018; 69 (5): 567–572)

**Key words:** symptomatic neuroendocrine tumours, lanreotide, cost analysis

## Streszczenie

**Wstęp:** Celem badania LanroNET była ocena wykorzystania zasobów medycznych oraz kosztów objawowego leczenia polskich chorych na nowotwory neuroendokrynnie z zastosowaniem lanreotydu autogel 120 mg.

**Materiał i metody:** LanroNET to wieloośrodkowe, nieinterwencyjne, obserwacyjne, prospektywne badanie przeprowadzone w 12 ośrodkach w Polsce. W badaniu uczestniczyli dorośli chorzy na wydzielające nowotwory neuroendokrynnie leczeni lanreotydem autogel 120 mg od przynajmniej 3 miesięcy przed włączeniem do badania. Podczas 24-miesięcznej obserwacji rzeczywistej praktyki klinicznej zbierano dane dotyczące wykorzystania zasobów medycznych oraz przebiegu terapii chorych z wydzielającymi nowotworami neuroendokrynnymi.

**Wyniki:** W badaniu uczestniczyło 54 chorych na wydzielające nowotwory neuroendokrynnie. Przeciętny czas stosowania lanreotydu wynosił 1,7 roku (zakres 0,0–2,2 lata). Badanie ukończyło 33 pacjentów, najczęstszą przyczyną przedwczesnego zakończenia leczenia (8/16) była progresja choroby. Całkowity średni koszt wykorzystanych zasobów bez kosztów farmakoterapii oszacowano na 26 307 zł/EUR 6 030,35 na pacjenta/rok. W czasie badania średni odstęp między wstrzyknięciami lanreotydu wynosił 31,7 dni (6,7). Pod koniec obserwacji, po 24 miesiącach od *follow-up*, 7 pacjentów stosowało 42-dniowe odstępy między dawkami. Średni rzeczywisty koszt lanreotydu autogel 120 mg wyniósł 4216,30 zł/966,49 EUR na pacjenta/28 dni we wspólnej perspektywie płatnika i pacjenta i był niższy o 554,16 zł/127,02 EUR niż koszt stosowania standardowych 28-dniowych odstępów między dawkami.

**Wnioski:** Badanie LanroNET jest pierwszym w Polsce obserwacyjnym dwuletnim badaniem chorych na czynne hormonalnie nowotwory neuroendokrynnie żołądkowo-jelitowo-trzustkowe oceniającym koszty codziennej praktyki klinicznej i koszty leczenia lanreotydem autogel. (Endokrynol Pol 2018; 69 (5): 567–572)

**Słowa kluczowe:** objawowe nowotwory neuroendokrynnie, lanreotyd, analiza kosztów



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## Introduction

Neuroendocrine tumour (NET) pharmacotherapy objectives are symptom control and the control of tumour progression. The long-acting analogues of somatostatin (lanreotide and octreotide) are used for the control of symptoms of hormonally active NET and tumour progression in advanced inoperable disease. The position in the therapy schemes of these two synthetic somatostatin analogues (SSA) is well established in current guidelines and recommendations [1–7]. According to the Polish Network of Neuroendocrine Tumours, SSAs are now indicated as a gold standard of symptomatic treatment of functional gastroenteropancreatic NETs (GEP-NETs) and recommended as the first-line therapy in midgut and pancreatic NET. Octreotide is recommended for the control of midgut NET G1 with low hepatic tumour load, while lanreotide is recommended in midgut and pancreatic NET G1 and G2 (Ki-67 index up to 10%) irrespective of hepatic tumour load [3–7].

The resource utilisation and cost of the treatment with lanreotide autogel 120 mg of symptomatic NETs in routine clinical practice were followed over 24 months. It provides evidence on the use of a drug in a real-life setting, which is a growing need for Polish payers and can serve to address multiple post-approval objectives. In contrast to some other countries, extended-dosing intervals (EDIs) with lanreotide autogel 120 mg (> 28 days) are licensed in Poland in symptomatic NET, which may have an impact on resource utilisation. This study, therefore, followed the real-world practice of lanreotide autogel 120 mg utilisation in patients with symptomatic NETs between mid-2012 and mid-2015. In April 2015 lanreotide autogel 120 mg was registered in Poland for the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) GEP-NET of the midgut, pancreatic, or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease. This registration was based on the CLARINET study results [8].

## Material and methods

The LanroNET study methodology was described previously [9]. LanroNET was a multicentre, non-interventional, longitudinal study conducted in Poland. Fourteen sites that treated eligible patients were contacted to propose participation, and two sites declined to participate. Eligible patients were adults with symptomatic NETs treated with lanreotide autogel 120 mg for at least three months before inclusion. The decision to initiate treatment with lanreotide autogel 120 mg was independent of the decision to enrol patients into the study. Patients terminating lanreotide treatment

during the follow-up were withdrawn from the study, with exception of less than eight weeks' break due to radioisotope therapy.

A sample size of 50 patients was estimated based on Polish epidemiological data, assuming that there were approximately 350 patients with symptomatic NET, and 18% of them were treated with lanreotide autogel 120 mg. It was considered that around 80% of eligible patients will consent to participate in the study. All consecutive patients were invited to participate in the study during inpatient and outpatient visits at the study sites.

Study visits, treatment monitoring procedures, and dose adjustments were made according to routine clinical practice at participating sites, up to 24 months after enrolment. The enrolment visit procedures included a review of relevant demographic characteristics, medical and treatment history, NET diagnostic characterisation and/or prior medication (therapies/surgeries for NET), NET symptoms, lanreotide autogel dose administered, aspects of administration (site of administration and person administering the drug), and injection intervals. The follow-up visit procedures included a review of current treatment details and changes in the treatment scheme and administration, and NET symptoms. Diagnostic procedures were recorded only if performed as part of a routine assessment during a visit. Adverse events (AEs) reporting followed regulations related to spontaneous reporting. Investigators were asked to report only related AEs. Study completion was defined as 24 months of follow-up completed, or the patients attended a visit that the investigator labelled as the last visit.

The primary objective of the LanroNET study was to assess the resource utilisation and cost of lanreotide autogel 120 mg when administrated as part of a routine treatment of NET symptoms.

All statistical analyses were descriptive. Six study sites provided unit costs; the mean of these costs was used in the base case scenario for each resource type (without weighting). In addition, sensitivity analyses were performed in which extreme scenarios were considered: minimum scenario (lowest unit cost) and maximum scenario (highest unit cost). The mean costs, and lowest and highest unit costs are presented in Supplementary Table S1.

Cost evaluation for lanreotide autogel 120 mg was performed from the perspective of the public payer in 2016 and patients, based on reimbursement status and retail price of Somatuline® Autogel from 1<sup>st</sup> June 2016, which was 4770.46 PLN/1093.52 EUR [10]. Costs in EUR were calculated based on the 2016 average PLN/EUR rate: 4.3625 PLN = 1 EUR [11]. Resource utilisation costs were assessed using a micro-costing approach. In the sensitivity analysis, the extreme scenarios were analysed: minimum

**Table I. Baseline characteristics and demographics of patients enrolled in the LanroNET study****Tabela I. Charakterystyka wyjściowa i dane demograficzne pacjentów włączonych do badania LanroNET**

Characteristic	Population (N = 54)
Age, mean ± SD, years	60.5 ± 0.7
Weight, mean ± SD, kg	73.6 ± 14.8
Male gender, n (%)	27 (50.0)
Performance status (ECOG–WHO), n (%)	NA = 2
0	19 (36.5)
1	22 (42.3)
2	9 (17.3)
3	2 (3.8)
4	0 (0.0)
Origin of NET, n (%)	
Gastrointestinal tract	27 (50.0)
Bronchopulmonary system	3 (5.6)
Pancreas	8 (14.8)
Colon/rectum	7 (13.0)
Unknown	9 (16.6)
Proliferation grading	NA = 10
G1	30 (68.2)
G2	10 (22.7)
G3	4 (9.1)
Ki-67 index categories	NA = 19
0–2%	27 (77.1)
> 2–20%	6 (17.1)
> 20%	2 (5.7)
Metastases present, n (%)	54 (100)
At multiple sites	45 (83.3)
Previous treatment for NET*, n (%)	
Surgery	46 (85.2)
Somatostatin analogues	43 (79.6)
Chemotherapy	6 (11.1)
PRRT	27 (50.0)
Medical history#, n (%)	
Hypertension	34 (63.0)
Diabetes	13 (24.1)
Cholelithiasis	4 (7.4)

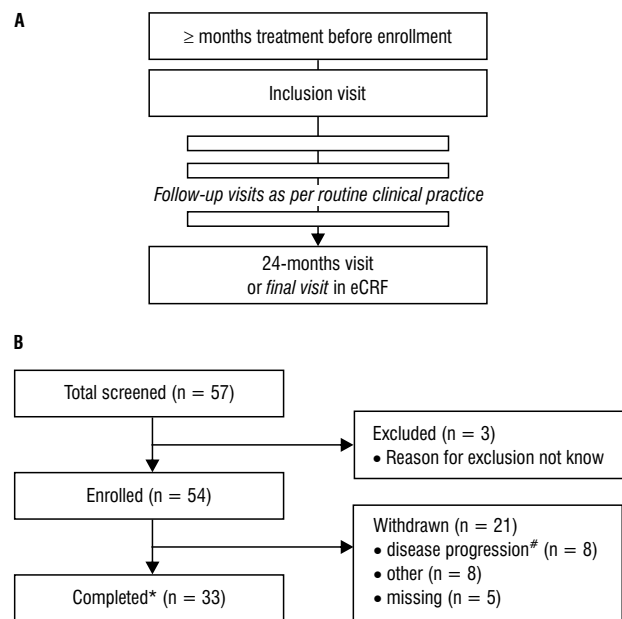
ECOG–WHO Eastern Cooperative Oncology Group–World Health Organisation, NA — not available (number of patients with data missing), PRRT — Peptide Receptor Radionuclide Therapy, SD — standard deviation; \*previous treatments include monotherapy and combination therapy; #patients could report more than one medical history event

scenario (with minimum values for unit cost) and maximum scenario (with maximum values for unit cost).

## Results

### Patients

Fifty-four patients with a mean age of 60.5 years, balanced between male and female (Table I) received lanreotide autogel 120 mg treatment for a mean (± SD) of 1.4 ± 0.7 years and median (range) 1.7 (0.0–2.2) years.



**Figure 1. Study design (A) and patient disposition (B);** \*either 24 months of follow-up completed (n = 26) or the investigator labelled visit as last (n = 7), #disease progression as recorded by the investigator (no further definition available)

**Rycina 1. Projekt badania (A) i przepływ pacjentów (B);** \*zakończone 24 miesiące obserwacji (n = 26) lub wizyta określona przez badacza jako ostatnia (n = 7), #progresja choroby oceniona przez badacza (brak dostępnej definicji)

Over 60% of the patients (n = 33, 61.1%) completed the study: n = 26 (48.1%) with 24 months of follow-up; n = 3 (5.6%) with last visit at 18 months; and n = 4 (7.4%) with last visit at 21 months. The most frequent recorded cause of discontinuation (8/21) was disease progression (Figure 1). Most patients scored 0 or 1 on the ECOG scale (Eastern Cooperative Oncology Group). Half of the patients had primary tumours located in the gastrointestinal tract. All enrolled patients presented metastases. At baseline, over two-thirds of patients (n = 30, 68.2%) presented with a well-differentiated tumour (G1) according to the WHO 2010 Classification [12]. Thirty-six (66.7%) patients reported at least one medical history at baseline (Table I).

Prior to study enrolment, 46 (85.2%) patients had undergone surgery. On average, the last surgery had occurred 4.6 ± 4.0 years before inclusion in the study. Forty-three (79.6%) patients had been treated with SSAs prior to the three-month pre-inclusion phase. Moreover, 27 patients (50.0%) had been previously treated with Peptide Receptor Radionuclide Therapy (PRRT).

### NET therapy during 24-month therapy with lanreotide autogel 120 mg

At baseline, 13% of patients did not report NET symptoms that could have resolved during the pre-inclusion

Table II. Annualised resource utilisation during lanreotide autogel 120 mg treatment

Tabela II. Roczne wykorzystanie zasobów podczas leczenia lanreotide autogel 120 mg

Resource type	Patients using resource $\geq 1$ *, n (%)	Annualised resource use Mean $\pm$ SD/ /year	Annualised cost — best case scenario	Annualised cost — minimum scenario	Annualised cost — maximum scenario
			Average cost/patient/year [PLN/EUR] (% of total cost)	Average cost/patient/year [PLN/EUR]	Average cost/patient/year [PLN/EUR]
Hospitalisations	40 (74.1)	6.98 $\pm$ 4.35*	24,214.00/5550.49 (92.04)	11,603.00/2659.71	99,190.00/22,736.96
Outpatient consultations	50 (92.6)	10.78 $\pm$ 2.28	1633.00/374.32 (6.21)	764.60/175.26	5,390.00/1235.53
Diagnostic procedures**	15 (27.7)	0.95 $\pm$ 0.46	116.00/26.59 (0.44)	13.92/3.19	1,421.00/325.73
Pathological markers			344.00/78.85 (1.30)	180.00/41.26	553.60/126.90
CgA	42 (77.8)	3.49 $\pm$ 2.42	140.00/32.09	132.00/30.25	411.00/94.21
5-HIAA	31 (57.4)	1.56 $\pm$ 1.36	80.00/18.33	12.55/2.87	78.38/17.96
Other***	1–14				
Total cost of resources consumed per patient per year (with exception of pharmaceuticals)			26,307.00/6030.26/(100)	12,552.00/2877.25	106,555.00/24,425.21

\*the number of patients using the resource at least once during the study. All prospectively recorded data was missing for 4 patients of 54 observed. These 4 patients stayed only one day in the study; \*\*diagnostic procedures include imaging of thorax, abdomen, and pelvis; \*\*\*other pathological marker tests used were for cortisol (n = 14), ACTH (n = 13), 5-HT (n = 8), insulin (n = 4), calcitonin (n = 3), gastrin (n = 2), and serum neuron-specific enolase (n = 1); \*one patient of 40 hospitalised patients stayed in the study for only one day and was not included in the analysis; PLN Polish zloty; EUR Euro

phase. The most frequent symptoms at baseline were abdominal pain, diarrhoea (n = 30 each, 55.6%), flushing (n = 27, 50%), and fatigue (n = 19, 35.2%). The proportion of patients affected by NET symptoms decreased over the course of the study. After 24-months 9/25 patients (36%) reported "none or improved" symptom(s). After 24-months of observation, diarrhoea was reported in 7/25 patients (28%), abdominal pain was reported in 4/25 patients (16%), and flushing was reported in 8/25 (32%) patients with available data at baseline and at 24 months.

At baseline, most patients with available data (n = 27, 77.1%) showed a Ki-67 index between 0% and 2%, which corresponds to a low proliferation index of the primary tumour (Table I). The mean concentration of chromogranin A (CgA) at baseline was 1140.98 ng/ml (indicative reference value: < 98 ng/ml [13]). The mean level of urinary 5-hydroxyindoleacetic acid (5-HIAA) was at baseline 37.51 mg/24 h (indicative reference value: 2–7 mg/24 h [14]).

Three patients experienced serious adverse events during the study. One patient experienced cholecystolithiasis and one patient experienced cholelithiasis. Both events were considered serious and related to lanreotide. One patient died 24 days after the last lanreotide administration due to cardiopulmonary failure in the context of advanced NET disease.

### Resource utilisation

The resource utilisation analysed during lanreotide autogel 120 mg treatment included hospitalisations, out-patient consultations, pathological marker tests, and diagnostic procedures (Table II). Forty patients

(74.1%) were hospitalised at least once. These patients were hospitalised on average (SD) 7.0 ( $\pm$  4.4) times per year. Moreover, each patient also consulted doctors a mean of 10.8 times per year (N = 50). In patients who underwent at least one diagnostic imaging procedure during the study (n = 15), the mean (SD) number of procedures per year was 0.95 ( $\pm$  0.46) (Table II). The most frequently used marker was CgA, with an average of 3.5 tests per year for the 42 patients who underwent at least one test. For 5-HIAA, the mean was 1.6 tests per year for the 31 patients with a minimum of one such test during the observation. Testing for insulin, calcitonin, gastrin, or serum neuron-specific enolase was done in 4, 3, 2, and 1 patient(s), respectively, during the study.

The total mean cost of consumed resources per patient per year was estimated at PLN 26,307/EUR 6030. Cost of hospitalisations represented 92.04% of the total cost, out-patient consultations contributed 6.21%, and pathological marker tests and diagnostic procedures accounted for 1.3% and 0.44%, respectively. The cost distribution in the minimum and the maximum scenarios was similar to that seen in the base case analysis (Table II).

### Lanreotide autogel 120 mg treatment and cost

The mean (SD) and median duration of lanreotide autogel 120 mg exposure was 1.4  $\pm$  0.72 and 1.7 years (range: 0.0–2.2), respectively (four patients remained in the study for only one day). At baseline nine patients (19.7%) were treated with lanreotide autogel 120 mg injection received at an EDI (> 4 weeks) (Table III). In the enrolled population, the mean number of days between injections was 31.7 (n = 50). Dosing regimen



Table III. Dosing regimen and cost of lanreotide autogel 120 mg

Tabela III. Schemat dawkowania i koszt lanreotide autogel 120 mg

Study time points	Dosing intervals, n (%)			Time between injections mean $\pm$ SD [days]	Annualised number of injections <sup>#</sup> mean $\pm$ SD	Average cost of treatment <sup>##</sup> mean/patient/28 days [PLN/EUR]
	4 weeks	6 weeks	8 weeks			
Baseline (n = 54)	45 (83.3)	8 (14.8)	1 (1.9)	31.68 $\pm$ 6.71	10.45 $\pm$ 2.56	4216.30/966.48
End of observation–24 months follow-up (n = 26)	19 (73.1)	7 (30.3)				

<sup>#</sup>four patients stayed only one day in the study, thus were not included into analysis. Five patients switched from lanreotide autogel 120mg to another NET treatment  
<sup>##</sup>common payer and patient perspective. Calculated according to price from the reference [10]

was extended (at HCP discretion) in four patients during first nine months after enrolment into the study. The proportion of patients treated with EDI increased during the study, and at the end of the 24-month observation 27% of patients were on a six-week dosing regimen (Table III). Two patients were on eight-week dosing frequency during the study. Five patients withdrew from the study after switching from lanreotide autogel 120 mg to another treatment: octreotide LAR (n = 2), PRRT (n = 2), and brachytherapy (n = 1). On average (SD), lanreotide autogel 120 mg was injected 10.5 ( $\pm$  2.6) times year. Drug administrations were performed in an outpatient setting (n = 450, 53.7%) and in a hospital (n = 387, 46.2%). All but one injection were made by nurses.

The mean cost of lanreotide autogel 120 mg per patient for a 28-day period (irrespective of regimen) was PLN 4212.5/EUR 965.61 and PLN 3.80/EUR 0.87 from the public payer and patient perspective, respectively (total PLN 4216.30/EUR 966.48; Table III).

## Discussion

In the study population, GEP-NETs were the most common (n = 42, 77.8%). At inclusion into the study patients were almost fully ambulatory as shown by their ECOG performance status. Every second patient underwent prior PRRT; however, it should be noted that PRRT procedures were historically developed and frequently used in Poland [15]. Over 60% of the enrolled patients completed the study. The most frequent reason for discontinuation of the treatment was disease progression, although information on how investigators defined progressive disease was not documented. According to recent guidelines, disease progression is not an indication to stop symptomatic treatment [3]. The percentage of patients negatively affected by NETs symptoms decreased to 36% during the two-year therapy. The safety profile of lanreotide autogel was similar to that reported in earlier studies in patients with functioning and nonfunctioning tumours [8, 16].

At the time of enrolment, lanreotide was approved for the symptomatic treatment of NETs only. In Polish

clinical practice, the registered indication allowed for the regular dosing interval of 28 days for lanreotide autogel 120 mg to be extended to 42 or 56 days, depending on the degree of symptomatic relief obtained, in the treatment of symptomatic NETs [16]. From the patient's perspective, medication administration modality and frequency are factors that influence therapeutic compliance, particularly in active patients with numerous priorities in their life [17]. In 2015, based on the results of the CLARINET study [8], showing a beneficial effect of lanreotide in reducing the risk of disease progression or death, lanreotide autogel 120 mg every 28 days was approved for the antitumoral treatment of GEP-NETs. The extended dosing regimens observed in LanroNET remain indicated for the symptomatic treatment of NETs only.

Real-world costs of SSAs, considered as the first-line symptomatic treatment of NETs, can be influenced by how they are used in clinical practice. The LanroNET study allowed prospective two-year follow-up of lanreotide autogel 120 mg regimens used, and observation of regular clinical practice to assess the treatment costs and resource utilisation in a real-life setting. It allowed a good estimation of economic aspects of the medical care provided to patients with functional NETs in Poland.

The mean cost of consumed resources per patient per year (excluding pharmaceuticals) was estimated at PLN 26,307/EUR 6030 and represented around 92% of the total cost (Table II). The relatively low cost of diagnostic procedures, contributing to less than 0.5% of the total mean cost, may indicate that monitoring of the disease by imaging examinations in real practice was not followed in line with guidelines that recommend it every 6–12 months in NET [3]. A small number of patients underwent a minimum of one diagnostic imaging procedure (n = 15) during the study, resulting in the diagnostic procedures annualised base case cost (Table II) being a few times lower than the mean unit cost (Supplementary Table S1). Treatment follow-up was focused mainly on clinical examination (outpatient visits) and biochemical marker determination.

The calculated annualised cost of therapy with lanreotide autogel 120 mg per 28-day period (all dosing regimens) was PLN 4212.50/EUR 965.61 and PLN 3.80/EUR 0.87 from the public payer and patient perspective, respectively. This cost was lower than the cost for calculated standard 28-day dosing regimen (PLN 4766.19/EUR 1092.53 and PLN 4.27/EUR 0.99, respectively), which suggests that the lanreotide autogel EDI is economically preferable in cases when symptom control can be achieved and maintained.

Today, use of lanreotide autogel 120 mg goes beyond symptomatic treatment of NETs. It should be noted that the antiproliferative effect of lanreotide is supported under the standard 28-day dosing regimen [8].

Pharmacoeconomic data comparing lanreotide autogel and octreotide LAR in GEP-NETs have been reported from an analysis of the PHARMO Record Linkage System in the Netherlands. On average, the patient cost was 7% less with lanreotide autogel than with octreotide LAR using a cost minimisation model. The driver of cost savings was the longer injection interval with lanreotide autogel. Mean injection intervals were 27 days for octreotide LAR and 31 days for lanreotide autogel [18]. Mean injection intervals observed in the Netherlands [18] and in the LanroNET study were similar.

The LanroNET study focused on resources, costs, and practical aspects of lanreotide autogel 120 mg utilisation. By its design and non-interventional nature, information about clinical outcomes of patients is limited. Many assessments were performed at the baseline visit (e.g. tumour proliferation), and in most cases were not assessed afterwards. Collected data concerned patients with symptomatic NETs receiving lanreotide autogel 120 mg for treatment of disease symptoms and should not be extended to the current broad use of the drug, which is the treatment of NETs through its antiproliferative activity.

## Conclusions

The LanroNET study is the first two-year observational study of patients with symptomatic NETs in Poland. It is also the first study evaluating such a long period of treatment with lanreotide autogel 120 mg in this patient population. The mean time between injections was longer than 28 days, reflecting the use of EDI in some patients and supporting the potential for lanreotide autogel 120 mg to reduce treatment burden and costs while treating the symptoms of NETs.

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